Pediatric Focused Safety Review: Nasonex® (mometasone furoate)

Pediatric Advisory Committee Meeting
May 7, 2012

Elizabeth L. Durmowicz, MD

Pediatric and Maternal Health Staff
Office of New Drugs

Center for Drug Evaluation and Research
Food and Drug Administration

Outline

- Background Information
- Clinical Studies
  - Treatment of Nasal Congestion Associated with Seasonal Allergic Rhinitis
  - Treatment of Nasal Polyps in Pediatric Patients
- Pediatric Labeling Changes
- Additional Relevant Safety Labeling
- Drug Use Trends
- Adverse Events
- Summary

Background Drug Information
Nasonex®
(mometasone furoate)

- **Drug:** Nasonex® (mometasone furoate)
- **Sponsor:** Schering
- **Therapeutic Category:** corticosteroid
- **Formulation:** nasal spray (50 mcg)
- **Original Market Approval:** October 1, 1997

Background Drug Information (continued)
Nasonex® (mometasone furoate)

- **Indications**:
  - Treatment of Allergic Rhinitis (patients ≥2 years)
  - Treatment of Nasal Congestion Associated with Seasonal Allergic Rhinitis (patients ≥2 years)
  - Prophylaxis of Seasonal Allergic Rhinitis (patients ≥12 years)
  - Treatment of Nasal Polyps (adults)

- **PREA Labeling Changes:**
  - May 26, 2010
    - New indication: nasal congestion associated with seasonal allergic rhinitis (patients ≥2 years)
  - January 19, 2011
    - Information from the pediatric nasal polyp trial

Nasal Congestion Studies

Nasonex®
(mometasone furoate)

- Safety and efficacy for the nasal congestion indication were established based on three randomized, double-blind, placebo-controlled, multicenter trials in 1008 patients ≥12 years with nasal congestion associated with seasonal allergic rhinitis (n=506 received Nasonex®).

- Efficacy in nasal congestion in patients 2-11 years was established based on extrapolation of efficacy from patients ≥12 years, and safety and efficacy were supported by studies of seasonal allergic rhinitis in patients 2-11years.

- No new safety signals were identified.

Pediatric Nasal Polyp Study

Nasonex®
(mometasone furoate)

- Safety and efficacy of Nasonex® in the treatment of nasal polyps in pediatric patients were evaluated in a randomized, placebo-controlled, double-blind, 4-month study in 127 patients 6-17 years. Patients were randomized to placebo, Nasonex® 100 mcg once or twice daily (patients 6-11 years) or 200 mcg once or twice daily (patients 12-17 years).

- Efficacy was not supported.

- No new safety signals identified.

The adult nasal polyp indication approved in December 2004.

Pediatric Labeling Changes-Nasal Congestion
Nasonex® (mometasone furoate)
May 2010

- Indications and Usage (1.2):
  - New indication (≥ 2 years)
- Dosage and Administration (2.2):
  - Dosing for patients 2-11 years and ≥12 years
- Adverse Events, Clinical Trial Experience (6.1):
  - Adverse events that occurred more frequently in patients treated with Nasonex® compared to placebo, i.e. sinus headache and epistaxis.
  - The overall adverse event profile was similar to that observed in the other allergic rhinitis trials.
- Clinical Studies (14.4):
  - Safety and effectiveness evaluated in 3 clinical studies in patients ≥12 years. Use in pediatric patients 2-11 years is supported by data from other pediatric clinical studies.

Pediatric Labeling Changes-Nasal Polyps
Nasonex® (mometasone furoate)
January 2011

- Pediatric Use (8.4):
  - Brief description of pediatric nasal polyp trial added.
  - The trial in pediatric patients did not support the efficacy of Nasonex® in the treatment of nasal polyps.
  - The adverse events were similar to adults.

* *The statement "safety and effectiveness for the treatment of nasal polyps in children < 18 years have not been established" retained from previous versions of labeling.*

Relevant Safety Labeling
Nasonex®
(mometasone furoate)

4 Contraindications:

Hypersensitivity to Nasonex® ingredients

5 Warnings and Precautions:

5.1 Local Nasal Effects:

Epistaxis, *Candida* Infection, Nasal Septum Perforation, Impaired Wound Healing

5.2 Glaucoma and Cataracts

5.3 Hypersensitivity Reactions

5.4 Immunosuppression

5.5 Hypothalamic-Pituitary-Adrenal Axis Effect

5.6 Effect on Growth

Relevant Safety Labeling (continued)
Nasonex®
(mometasone furoate)

6 Adverse Reactions

6.1 Clinical trial experience in patients with allergic rhinitis < 12 years and ≥12 years

8 Use in Specific Populations

8.4 Pediatric Use: Reduction in growth velocity

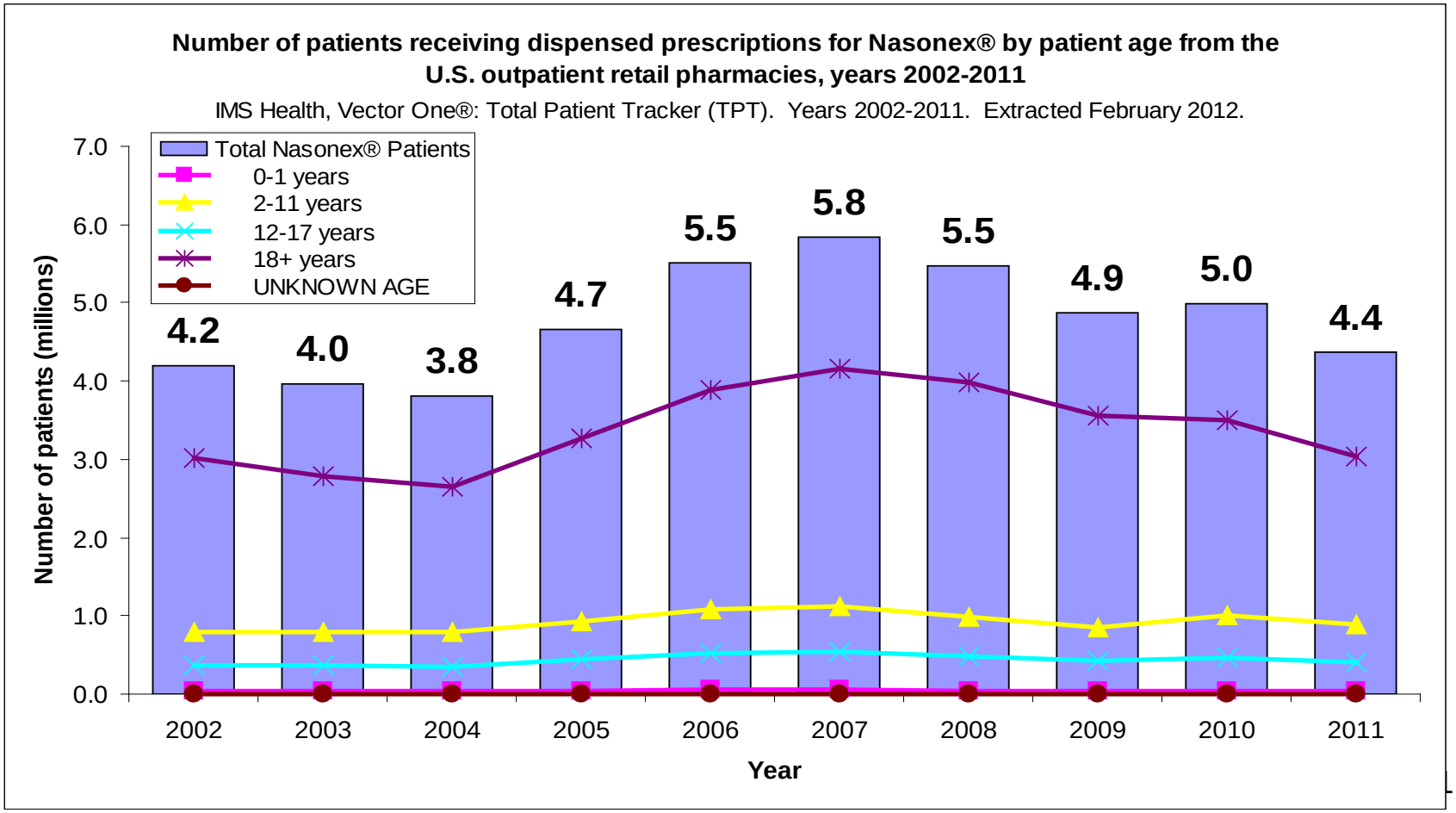
12 Clinical Pharmacology

12.2 Pharmacodynamics: Describes adult and pediatric studies evaluating adrenal function

17 Patient Counseling Information

Nasonex® Drug Utilization

Patient Count by Patient Age:



Nasonex® Drug Utilization (continued)

Total Prescription and Patient Counts by Patient Age (Y2011)*:

	Total	≥18 years	12-17 years	2-11 years	0-1 years
Prescriptions (Rx)	8,079,523 (100%)	6,082,617 (75%)	606,634 (7.5%)	1,339,911 (17%)	49,792 (<1%)
Patients receiving Rx	4,371,490 (100%)	3,030,192 (69%)	414,310 (9.5%)	885,274 (20%)	39,936 (<1%)

**Source: IMS Health, Vector One®: National (VONA) and Total Patient Tracker (TPT). Year 2011. Data extracted February 2012.*

Top Diagnosis All Age Groups (Years 2002-2011, cumulative)**:

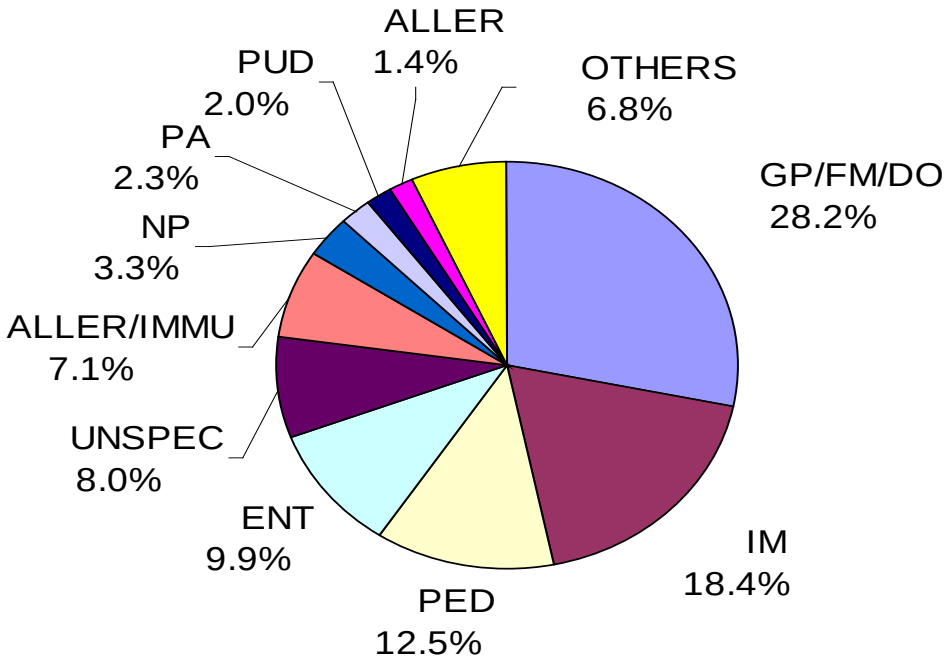
"Allergic Rhinitis NOS" (ICD-9 code 477.9) and "Chronic Sinusitis NOS" (ICD-9 code 473.9)

***Source: SDI, Physician Drug and Diagnosis Audit™. Years 2002-2011. Data extracted February 2012.*

Nasonex® Drug Utilization (continued)

Top 10 Prescribing Specialties:

Number of dispensed prescriptions for Nasonex® by the top 10 prescribing specialties from the U.S. outpatient retail pharmacies, cumulative years 2002-2011



Source: IMS Health, Vector One®: National (VONA). Years 2002-2011. Data extracted February 2012.

Total Number* Nasonex® Adverse Event Reports

(January 1, 2002 to December 31, 2011)

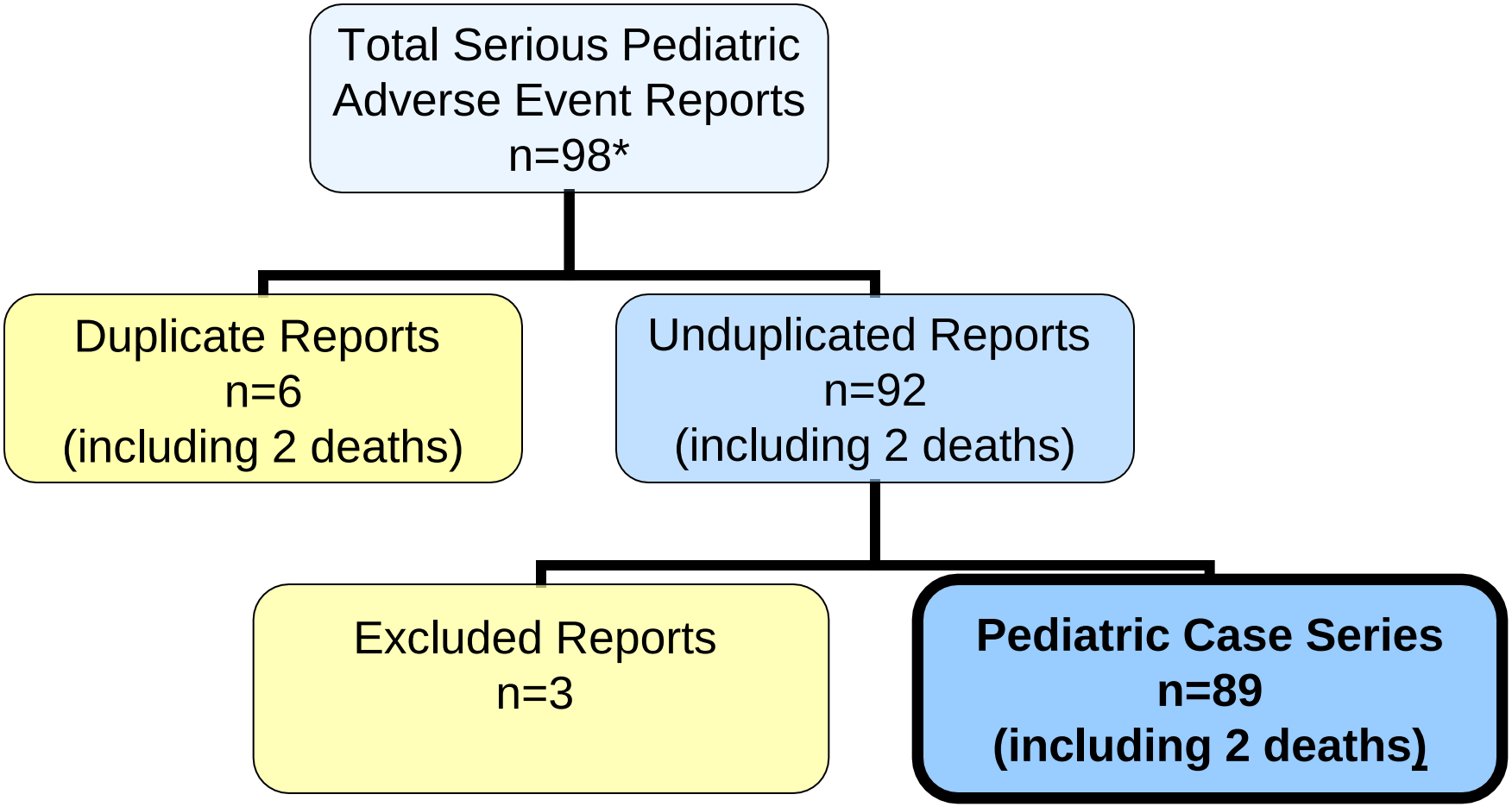
	All reports (US)	Serious**(US)	Death (US)
Adults (≥ 17 yrs.)	502 (286)	431 (221)	11 (5)
Pediatrics (0-16 yrs.)	**103 (56)**	**97 (50)**	**3 (1)**
Unknown Age (Null values)	236 (161)	202 (128)	30 (27)***
Total	841 (503)	730 (399)	44 (33)

* Not assessed for causality and may include duplicates

**Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening events, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.

***One pediatric report (duplicate from pediatric death series)

Nasonex® Adverse Event Reports Case Selection



**Includes all pediatric serious outcomes (n=97) and age unknown pediatric death (n=1)*

Characteristics of Serious Pediatric Cases
Nasonex® (n=89)

- Age (n=89)
  - 0-1 month* (n=4)
  - 1 month < 2 years** (n=4)
  - 2-5 years (n=21)
  - 6-11 years (n=36)
  - 12-16 years (n=24)

  **In-Utero exposure; **Unapproved age group: <2 years*

- Daily Dose (n=26)
  - Mean: 100 mcg
  - Range: 50 – 200 mcg

- Duration of Therapy (n=42)
  - Mean: 114 days
  - Median: 27 days
  - Range: 1-1825 days

Serious Adverse Events

Nasonex® (n=89)

- Fatal Serious Events (n=2)
- Serious Non-Fatal Adverse Events (n=87)
  - Central Nervous System and Psychiatric Events (n=27)
  - Respiratory Events (n=11)
  - Vision Disorders (n=11)
  - Hypersensitivity Reactions (n=10)
  - Gastrointestinal Events (n=5)
  - Hearing Disorders (n=5)
  - In Utero Exposure (n=4)
  - Metabolic Events (n=3)
  - Musculoskeletal Events (n=3)
  - Renal and Hematologic Events (n=3)
  - Infections (n=2)
  - Other Miscellaneous (n=3)

Unlabeled adverse events are underlined on all slides.

(Review did not identify other events of interest, i.e. epistaxis, nasal ulceration, Candida infection, nasal septal perforation, impaired wound healing, worsening of infections, glaucoma or cataracts, reduction in growth velocity, hypercorticism, adrenal suppression)

Fatal Serious Adverse Events

Nasonex® (mometasone furoate)

Fatal Events (n=2)

7 year male with a fatal asthma attack at time of initiation of lansoprazole* for gastroesophageal reflux. Patient experienced chest tightness, collapsed and died. Autopsy noted eosinophilic bronchitis and mucus plugging, and concluded death "likely due to status asthmaticus". Other medications: budesonide/formoterol aerosol**, Nasonex®, and montelukast*.

**Lansoprazole and montelukast labeled for anaphylactic reactions. ** Budesonide/formoterol aerosol labeled for asthma-related death.*

9 year male "died due to" dizziness, dyspnea, dysstasia, eye movement disorder, gastric dilation, and increased weight. Medications: quetiapine, haloperidol, olanzapine, sertraline, methylphenidate, atomoxetine, clonidine, fluticasone inhaler, Nasonex®, albuterol HFA.

**Concomitant medications labeled for dizziness, dyspnea, muscle weakness, vertigo, postural hypotension, nystagmus, weight gain, and suggest confounding medical history.*

Both cases confounded by concomitant medications and other pre-existing or coexisting morbidities.

Serious Adverse Events

Nasonex® (mometasone furoate)

Central Nervous System and Psychiatric Events (n=27)

Neuropsychiatric Events (n=12):

- Aggression (n=6)
  - Causality unable to be assessed* (n=6)
- Behavior Problems (n=3)
  - 2 year male with increased irritability and temper tantrums after 1 week Nasonex® 100 mcg at bedtime. Resolved with discontinuation, recurred with restart of Nasonex® and resolved with discontinuation.
  - 7 year male initiated Nasonex® and developed behavior problems and trouble swallowing. Hospitalized x1 week for swallowing. Psychiatric evaluation did not determine cause of the behaviors. Nasonex® discontinued and behavior improved. Later restart of Nasonex® resulted in recurrence of behavior problems which resolved with discontinuation.
  - Causality unable to be assessed* (n=1)

**Causality unable to be assessed due to pre-existing medical disorders, concomitant exposure to steroids, and insufficient clinical information (n=9 Neuropsychiatric Events)*

Serious Adverse Events (continued)

Nasonex® (mometasone furoate)

Neuropsychiatric Events (continued)

- Multiple Psychiatric Symptoms (n=1)

  6 year male with 'depressed effect', 'suicidal thoughts', 'anxiety attacks', and 'hypochondriac behavior' x 5 weeks after discontinuation of Nasonex® 50 mcg twice daily. Medications included montelukast and Xopenex®**.

  **Montelukast labeled for neuropsychiatric events, including suicidality. **Xopenex ® labeled for anxiety, nervousness*

- Irritability* (n=1)
- Hallucinations* (n=1)

  Causality unable to be assessed due to pre-existing medical disorders concomitant exposure to steroids, and insufficient clinical information (n=9 Neuropsychiatric Events).

Seizures (n=9)

- Convulsions (n=4)
- Epilepsy (n=4)
- Stuttering (n=1)

Serious Adverse Events (continued)

Nasonex® (mometasone furoate)

Seizures (continued)

Patients without a history of seizures (n=4):

- 8 year male with "anxiety attack", i.e. convulsions, hallucinations, dilated pupils, loss of body control, and night terrors for 10-15 minutes (x1), and shorter duration (x4) on one night. Medications: Nasonex®, Singulair®*, Zyrtec®, and occasional Protopic®. Nasonex® discontinued.

  **Singulair labeled for neuropsychiatric events, including seizures, hallucinations, dream abnormalities.*

- 9 year male with headaches and possible seizure, i.e. eyes rolling back, protruded tongue, and jerky movements, after 1 year intermittent Nasonex®. Recurrence of events with Nasonex® restart. Neurology evaluation pending.
- 4 year male with hyperactivity, then staring, disorientation and no engagement in conversation 30 minutes after day 2 of Nasonex®. Emergency Dept. exam normal. Nasonex® not suspect. Neurology evaluation recommended.
- 7 year male with suspected epilepsy (and planned EEG), developed a "prickle in the mouth", stuttering and incomprehensible words x 1 minute after 1 month Nasonex® use.

Serious Adverse Events (continued)

Nasonex® (mometasone furoate)

General Central Nervous System (CNS) Events (n=6)

- Memory Loss (n=2)
  - 13 year male with disorientation, nervousness, and memory loss during Nasonex®, azithromycin*, and sodium dipyrone** treatment for sinusitis and fever. Nasonex® temporarily discontinued. Disorientation and nervousness resolved. Memory loss outcome unknown.

    **Azithromycin labeled for nervousness, dizziness/vertigo. **Sodium dipyrone not approved in US.*

  - 16 year male with 24 hour memory loss while using Nasonex® and azelastine nasal spray*. Normal CT. Minimal additional information.

    **Azelastine labeled for somnolence, impairment of CNS performance.*

- One report each: Right facial paralysis; Malaise/Loss of consciousness; Hypoesthesia; Autism

Serious Adverse Events (continued)

Nasonex® (mometasone furoate)

Vision Disorders (n=11)

- Papilledema (n=4)

  (Intracranial hypertension also reported: n=3)

  – 5 year female with fever, sore throat developed headache, blurred vision, and vomiting. CT normal except sinusitis. Diagnosed with papilledema and intracranial hypertension. Medications included beclomethasone inhaler, salmeterol, mometasone nasal, clarithromycin, desloratadine.

  – 13 year female with eye pain, diagnosed with papilledema and benign intracranial hypertension. Medications: desloratadine, Nasonex®.

  – 12 year male on somatropin* and Nasonex® with papilledema diagnosed with psuedotumor cerebri. Somatropin discontinued. Papilledema resolved.

  **Somatropin labeled for intracranial hypertension*

  – 16 year male with history of tick bite, encephalitis and eye surgery on Nasonex® with "unsharp papilla". Nasonex® discontinued. "Papilledema" continued.

- Cataract (n=2)
- One report each: glaucoma; intraocular pressure increased; strabismus and diplopia; corneal disorder; temporary vision loss.

Intracranial hypertension, papilledema and temporary vision loss are unlabeled (n=5).

Serious Adverse Events (continued)

Nasonex® (mometasone furoate)

Respiratory Events (n=11):

- Bronchial hyperreactivity; Bronchospasm; Epistaxis; Anosmia/parosmia; Nasal septum perforation (n=2)
- Cough (n=1)

All respiratory events are labeled.

Hypersensitivity Reactions (n=10)

- Rash (n=3)
- Swollen tongue (n=2)
- One report each: solar urticaria; hypersensitivity syndrome; lip swollen; glossodynia; tachycardia

Although glossodynia is an unlabeled event, the other hypersensitivity events are labeled or appear to be confounded.

Gastrointestinal Events (n=5)

- One report each: “stomach upset”; constipation; diarrhea; diarrhea and red stools; cramps.

Serious Adverse Events (continued)
Nasonex® (mometasone furoate)

Hearing Disorders (n=5)

- Earache (n=3)
- One report each: Hearing loss; Tympanic membrane perforation (due to trauma)

Metabolic Events (n=3)

- Weight gain (n=2)
  - 5 year female with 26 lb. weight increase (over an unknown time period) while on Nasonex® 100 mcg per day to treat allergy and sleep apnea. Nasonex® discontinued. Restart resulted in 4 lb. weight increase in 4 weeks. Concomitant medication: desloratadine* x 15 days.

    **Desloratadine labeled for edema.*
  - 10 year female on Nasonex® with 10lb weight gain (over an unknown time period).
- Hyperglycemia (n=1)

Serious Adverse Events (continued)

Nasonex® (mometasone furoate)

Musculoskeletal Events (n=3)

- Growth retardation (n=2)

  Both cases

  – Confounded by concomitant inhaled corticosteroids, i.e. 2 years and 4 years
  – Reported laboratory values consistent with adrenal insufficiency
- Jaw pain (n=1)

Renal and Hematologic Events (n=3)

- Elevated hepatic enzymes (n=2)
  – 5 year male admitted for elevated liver enzymes. Concomitant medication: loratadine. No additional details.
  – 23 month male with elevated ALT and AST. Liver biopsy planned. Concomitant medications: cetirizine and tetrahydrozoline nasal.
- Proteinuria:

Serious Adverse Events (continued)

Nasonex® (mometasone furoate)

Infections (n=2)

- Upper Respiratory Tract Infection/Fever
- Peritonsillar abscess, followed by “fungus bulla” of the maxillary sinus.

Other Serious Miscellaneous (n=3)

- One report each: Bradycardia; Heart attack; Lack of effect

Summary Pediatric Focused Safety Review

Nasonex® (mometasone furoate)

- The pediatric safety review identified 89 foreign and domestic serious adverse event reports, including 2 reports of death over a **ten** year period.
- Per Utilization Data, approximately 2 million Nasonex® prescriptions were dispensed to approximately 1.3 million pediatric patients in the US in 2011.
- The majority of the reports were labeled events and single case reports.
- Interpretation of the unlabeled events was limited by conflicting information, incomplete case descriptions, underlying medical disorders and concomitant medications.
- No new safety signals were identified.
- FDA recommends continued routine postmarketing monitoring.
- Does the Committee concur?

ACKNOWLEDGEMENTS

DPARP
Sandra Barnes
Anthony Durmowicz, MD
Xu Wang, MD, PhD
Badrul A. Chowdhury, MD, PhD
Sally Seymour, MD

PMHS
Lisa L. Mathis, MD
Denise Pica-Branco, PhD
Hari Cheryl Sachs, MD

OPT
Judith Cope, MD, MPH
Diane Murphy, MD
Amy Odegaard, MPH
Pamela Weinel, RN, MSN, MBA

OSE
Ethan D. Hausman, MD
Dipti Kalra, RPh
Ann Corken-Mackey, RPh, MPH
Laura Governale, Pharm.D., MBA
Hina Mehta, PharmD
Tracy Pham, PharmD
Linda J. Scarazzini, MD, RPh
Judy Staffa, PhD, RPh